REMARKS

This is a full and timely response to the outstanding nonfinal Office Action mailed August 23, 2006. Reconsideration and allowance of the application and presently pending claims, as amended, are respectfully requested

Present Status of Patent Application

Upon entry of the amendments in this response, claims 1-4 and 23-32 are pending in the application. Claims 5-22 are cancelled. Claim 1 and 2 have been amended herein, and claims 23-32 have been newly added. Claims 1-4 are objected to due to an informality. Claims 1-4 stand rejected under 35 U.S.C. §103.

The prior art made of record has been considered, but is not believed to affect the patentability of the presently pending claims. Applicants believe that no new matter has been added and that a new search is not necessary. Applicants respectfully request reconsideration and withdrawal of these objections and rejections for the reasons discussed below.

Claim Objection

Claims 1-4 are objected to due to an informality. Namely, the Examiner states that in claim 1, line 21, □-carbon should be α-carbon. Applicants have amended Claim 1 to recite "α-carbon". Applicants therefore submit that the objection has been overcome.

Claims Rejections Under 35 U.S.C. §103

Claims 1-4 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Saatman et al. (*Proc. Natl. Acad. Sci. USA*, 1996, 93, 3428) (hereinafter "Saatman") in view of Wang, et al. (*J. Neuropathol. Exp. Neurol.*, 2000, 59, 599) (hereinafter "Wang") and Schaecher et al. (*Naurochem. Res.,* 2001, 26, 731) (hereinafter "Schaecher"). Applicants respectfully traverse.

Discussion of Wang and Saatman

Claim 1, as amended, reads in pertinent part as follows:

> A method for treating ***axonal degeneration of the peripheral nervous system of a patient*** comprising: ***administering to the patient*** a compound of the formula:
>
> M^1-AA^2-AA^1-CO-NR_3R_4
>
> a pharmaceutically acceptable salt or prodrug thereof...in an amount sufficient to ***treat axonal degeneration***.

[Emphasis added]. Applicants respectfully submit that neither Saatman nor Wang, taken alone or in combination, teach at least the highlighted portions of claim 1 above.

In particular, Saatman does not teach the treatment of ***axonal degeneration of the peripheral nervous system (PNS)***. Instead, Saatman teaches the use of AK295 in the treatment of neuronal loss in the central nervous system (CNS) due to major head trauma. Applicants submit the Declarations of the inventors, Dr. James Powers (Exhibit A, paragraph 9) and Dr. Jonathan Glass (Exhibit B, paragraph 9) as evidence that those of skill in the art would understand that since the neuronal cell body and the axon are biologically separate structures that respond differently to various stimuli (see Exhibit D), treatment of neuronal cell trauma does not predict whether AK295 would be effective in treatment of axonal degeneration for peripheral neuropathy (PN).

While Wang teaches the *in vitro* use of AK295 to inhibit axotomy and vincristine-induced axonal degeneration, it does not teach the claimed *in vivo* method of treating axonal degeneration of the ***peripheral nervous system of a patient*** by administering to a patient an amount of a compound, such as AK295. Since evidence that a compound is useful to treat one disorder is not necessarily suggestive that a compound will be useful to treat other disorders effected by different biological mechanisms and since it is well known that a compound that is active in vitro may not have the same (or any) activity in vivo, Wang, alone or in combination with Saatman, does not teach or suggest the claimed method. Furthermore, Applicants submit the Declarlaration of Dr. Jonathan Glass, inventor of the claimed invention and author of the Wang reference, who states that it was not obvious to him whether AK295 would provide effective *in vivo* inhibition of axonal degeneration in a whole animal model, nor would it have been in view of the teachings of Saatman (Exhibit B, paragraph 10).

Thus, neither the teachings of Wang nor Saatman render obvious the *in vivo* use of AK295 to treat axonal degeneration in a patient. Furthermore, since axonal degeneration of the PNS and neuronal loss in the CNS represent very different biological mechanisms, one of skill in the art would not be likely to look to Saatman for guidance for the *in vivo* treatment of axonal degeneration of the PNS. Moreover, significant secondary considerations (such as the skepticism of others in the art, and long felt need) demonstrate the nonobviousness of the claimed method.

Pertinent Secondary Considerations Support a Conclusion of Nonobviousness

Applicants maintain that pertinent secondary considerations support a conclusion of non-obviousness, and provide the attached declarations of the inventors Dr. James Powers (Exhibit A) and Dr. Jonathan Glass (Exhibit B) and skilled artisan Dr. Raymond Bartus (Exhibit C) as evidence of such secondary considerations.

The Supreme Court stated that objective evidence or secondary considerations (*e.g.*, long-felt need, failure of others, skepticism of others, *etc.*) must be considered by the Patent Office when determining obviousness under 35 U.S.C. §103. *See* Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966).

First, even in view of the teachings of Saatman and Wang, it would not have been obvious to one of skill in the art to use AK295 for the *in vivo* treatment of axonal degeneration of the PNS because of skepticism of others skilled in the art as to the effectiveness of AK295 *in vivo*. As stated in the declarations of Drs. Powers and Glass (see Exhibits A and B, paragraphs 11 and 12), such skepticism almost led the inventors to abandon the pursuit of AK295 as a treatment for axonal degeneration. In particular, they were discouraged by the opinion expressed by Dr. Raymond Bartus (see Exhibit C, paragraph 8), who has extensive experience working with AK295. Dr. Bartus expressed the belief that AK295 would not work for the treatment of axonal degeneration in peripheral neuropathy because it would not be orally active. He indicated that he did not think it was possible to administer AK295 to an animal in a therapeutically practical manner to have sufficient bioavailability in the nervous system to have a significant effect on a condition such as peripheral neuropathy. The opinion of Dr. Bartus, a known expert in the field with direct experience with AK295, supports the nonobviousness of the claimed methods.

In addition, Applicants supply evidence in support of the secondary considerations that there was a long felt need in the art for a viable treatment for peripheral neuropathy associated with axonal degeneration and that no viable alternatives exist. As set forth in paragraph 14 of the declarations of Drs. Powers and Glass (exhibits A and B, respectively), peripheral neuropathy due to axonal degeneration is a major neurological illness affecting millions of people worldwide. PN is the most frequent, and often dose-limiting, neurotoxic side effect of drugs (such as many commonly used anti-cancer agents) used for a wide spectrum of human diseases. In addition, common diseases such as diabetes mellitus, HIV infection, auto-immune disorders, and cancer are also frequently complicated by the onset and progression of debilitating

peripheral neuropathies. These diseases, as well as many of the drugs that induce PN, have been in existence for decades. The foregoing therefore establishes that an urgent need for a treatment for PN has long existed.

The declarants further establish that no suitable alternative treatments currently exist for the treatment of axonal degeneration that causes PN (exhibits A and B, paragraph 15). Current treatment of axonal degeneration neuropathies consists primarily of palliation of pain with analgesics and physical and occupational therapy for management of disability. No satisfactory treatment for repairing or preventing the axonal degeneration, other than discontinuing a drug causing the PN, currently exists. Since the offending drug is often necessary for the treatment of a serious (often lift-threatening) disease, discontinuation is often not an option. Therefore, the treatment of PN caused by axonal degeneration represents both a long-felt and unmet need.

Furthermore, Applicants submit that the cited references themselves also provide evidence of a long felt but unsolved need in support of a conclusion of nonobviousness. The Saatman reference has a priority date of 1996, which is at least 6 years prior to the filing of the pending application. The Wang reference has a priority date of 2000, which is at least 2 years prior to the filing of the pending application. This demonstrates that the separate technologies have coexisted for over 2 years before the filing of the pending application. Furthermore, the compound AK295 has existed since 1994, at least 8 years prior to the filing of the pending application. However, during this period, Drs. Powers and Glass are not aware of the use of either AK295 or any other calpain inhibitor for the treatment of axonal degeneration of the peripheral nervous system of a patient. Applicants submit that this period of years is indicative of the nonobviousness of claim 1 because, if the combination of Saatman with Wang was as obvious as the Office Action alleges, it is unlikely that there would have been such a long period of dormancy before Applicants' invention.

In view of the foregoing secondary considerations, it is apparent that the Office Action has failed to sufficiently establish that the claimed methods of treating axonal degeneration were obvious to one of ordinary skill in the art as of the effective filing date for the instant application. Thus, Applicants respectfully request that the 35 U.S.C. §103 rejection of claims 1-4 be withdrawn.

Applicants respectfully submit that dependent claims 2-4 and 23-25 include every feature of independent claim 1. Thus, pending dependent claims 1-4 are allowable over

the prior art of record for at least the reasons set forth for claim 1, above. *In re Fine*, 5 U.S.P.

Although claim 2 stands further rejected as allegedly unpatentable over Saatman in view of Schaecher, Applicants submit that claim 2 is allowable for all of the reasons recited for claim 1, above. Applicants further submit that claim 2 is independently allowable over Saatman in view of Schaecher for at least the reason that protection against degeneration of myelin proteins (as suggested in Schaecher) is completely different than protection against degeneration of axons as set forth in claim 2 (see declaration of Dr. Glass, Exhibit B, paragraph 16).

Applicants further submit that new claims 26-32, drawn to a method for treating axonal degeneration of the peripheral nervous system of a mammalian host administering to the mammalian host an effective amount compound of the formula M^1-AA^2-AA^1-CO-NR_3R_4, a pharmaceutically acceptable salt or prodrug thereof, are also allowable over the prior art of record for the same reasons as set forth for claims 1-4 above.

CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicants respectfully submit that all rejections have been traversed, rendered moot, and/or accommodated, and that the now pending claims 1-4, and 23-32 are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned agent at (770) 933-9500.

Respectfully submitted,

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